**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Patent Application No. 10/521,930

Applicant: Boyd et al.

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Examiner: Rahmani, N.

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Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**DECLARATION UNDER 37 C.F.R. § 1.132 OF MICHAEL R. BOYD**

I, Michael R. Boyd, do hereby declare as follows:

1. I received a Bachelor of Science degree in Chemistry, with honors, in 1969 from the University of Kentucky, a Doctor of Medicine degree in 1975 from Vanderbilt University, and a Doctor of Philosophy degree with a major in Pharmacology and a minor in Organic Chemistry in 1975 from Vanderbilt University.

2. Since 2002, I have been the Abraham A. Mitchell Chair and Director of the USA Mitchell Cancer Institute and Professor of Medicine and Pharmacology in the College of Medicine at the University of South Alabama in Mobile, Alabama.

3. Prior to my current position, I was employed as a Staff Fellow in the Pharmacology/Toxicology Research Associate (PRAT) Program at the National Institute of General Medical Sciences and Laboratory of Chemical Pharmacology, National Heart, Lung and Blood Institute, in Bethesda, Maryland from 1975-1977, as a Senior Investigator of the

Clinical Pharmacology Branch of the Clinical Oncology Program in the Division of Cancer Treatment at the National Cancer Institute in Bethesda, Maryland from 1977-1978, as Head of the Molecular Toxicology Section of the Clinical Pharmacology Branch of the Clinical Oncology Program in the Division of Cancer Treatment at the National Cancer Institute in Bethesda, Maryland from 1978-1981, as Chief of the Laboratory of Experimental Therapeutics and Metabolism of the Developmental Therapeutics Program in the Division of Cancer Treatment at the National Cancer Institute in Bethesda, Maryland from 1981-1984, as Associate Director for Developmental Therapeutics in the Division of Cancer Treatment at the National Cancer Institute in Bethesda, Maryland from 1984-1990, as Chief of the Laboratory of Drug Discovery Research and Development of the Developmental Therapeutics Program in the Division of Cancer Treatment at the National Cancer Institute in Bethesda, Maryland from 1990-2001, and as Director of the Molecular Targets Development Program in the Division of Cancer Treatment at the National Cancer Institute in Bethesda, Maryland from 2001-2002.

4. I am licensed to practice medicine by the State Licensing Boards of Tennessee and Maryland.

5. I am the author or co-author of over 450 research papers, as well as numerous reviews and book chapters. I am a coinventor on numerous patents and patent applications, including the present patent application. I have been an invited speaker at numerous national and international scientific meetings, hold membership in many scientific organizations, serve on the Editorial Boards of several major scientific journals, and am the recipient of at least eleven awards for Achievement and Meritorious Service in the sciences as set forth in the attached Curriculum Vitae and Bibliography.

6. At the time the subject patent application was filed, I was actively engaged in scientific research in the field of art to which the instant patent application pertains. I am aware of the general knowledge available in the art and of the skill level of the ordinary artisan as it exists today and as it existed at the time the instant patent application was filed.

7. Synthetic methods of preparing compounds of formula (I) by direct methods or modification of poecillastrin A are described in the instant specification. Methods are fully described in the specification and were considered a routine and ordinary practice at the time the instant patent application was filed. See, for example, page 12, line 14 through page 13, line 31 of the specification. In a specific example, the specification describes how to make the compounds of formula (I) by chemically modifying various oxygen- and nitrogen-containing groups (e.g., conversion of a hydroxyl group to an ester with an esterifying agent, such as an anhydride or acid chloride).

8. The specification also describes the isolation, purification, and determination of chemical structure of a compound of formula (I). It would have been well-within the skill of the ordinary artisan at the time the instant patent application was filed to perform such steps to prepare and characterize a claimed compound of formula (I). See, for example, page 29, line 31 through page 31, line 32 of the specification.

9. The specification also identifies methods for determining the vacuolar-type (H+)-ATPase inhibitory activity and cytotoxicity for compounds of formula (I). See the specification at, for example, page 19, line 6, to page 29, line 30. More specifically, Example 3 illustrates the general procedure for obtaining the activity profile of exemplary compounds of the invention using the NCI 60 cell-line screen. The NCI 60 cell-line screen is available for public researchers. Examples 4-6 illustrate the vacuolar-type (H+)-ATPase inhibitory activity and cytotoxicity of compounds of the invention (e.g., an extract of *Poecillastra* species and poecillastrin A). Exemplary conditions that are susceptible to prevention or treatment by a compound of formula (I) are fully described in the specification and were well known in the art at the time the present application was filed. See the specification at, for example, page 16, line 27, to page 18, line 7. The results of my research have been published in Bowman, E. J., Gustafson, K. R., Bowman, B. J., Boyd, M. R., Identification of a New Chondropsin Class of Antitumor Compound that Selectively Inhibits V-ATPases, *J. Biol. Chem.*, **2003**, *278*, 44147-44152, a copy of which is attached. Given the teachings in the

specification of the biological activity and utility of the compounds of formula (I), one of ordinary skill in the art would readily know how to use the claimed compounds.

10. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 9/27/06

Michael R. Boyd, M.D., Ph.D.

May, 2006

**Curriculum Vitae**

NAME: Michael R. Boyd, M.D., Ph.D.

DATE & PLACE OF BIRTH: July 5, 1947, Cookeville, Tennessee

CITIZENSHIP: United States

MARITAL STATUS: Married, no children

EDUCATION:

| | |
|---|---|
| May 1965 | Graduated from high school |
| May 1969 | B.S., Honors, Chemistry, University of Kentucky |
| May 1975 | Ph.D., Pharmacology and Organic Chemistry, Vanderbilt University |
| May 1975 | M.D., Vanderbilt University, School of Medicine |

MEDICAL LICENSURE:

Current medical licensure in states of Tennessee (License Reg. No. MD0000009357) and Maryland (License Reg. No. D0024880); U.S. Controlled Substance Registration Certificate AB9301235

OTHER LICENSURE:

Licensed Commercial Pilot; FAA Certificated Flight Instructor

POSITIONS HELD:

| | |
|---|---|
| 1975-1977 | Staff Fellow, Pharmacology/Toxicology Research Associate Program, National Institute of General Medical Sciences, and Laboratory of Chemical Pharmacology, National Heart, Lung and Blood Institute, National Institutes of Health (NIH), Bethesda, Maryland |
| 1977-1978 | Senior Investigator, Clinical Pharmacology Branch, Clinical Oncology Program, Division of Cancer Treatment, National Cancer Institute (NCI), Bethesda, Maryland |
| 1978-1981 | Head, Molecular Toxicology Section, Clinical Pharmacology Branch, Division of Cancer Treatment, NCI, Bethesda, Maryland |
| 1981-1984 | Chief, Laboratory of Experimental Therapeutics & Metabolism, Division of Cancer Treatment, NCI, Bethesda, Maryland |

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|---|---|
| 1984-1990 | Director, Developmental Therapeutics Program; Associate Director, Division of Cancer Treatment, NCI, Bethesda, Maryland |
| 1990-2001 | Chief, Laboratory of Drug Discovery Research & Development, Division of Cancer Treatment & Diagnosis, NCI, Bethesda, Maryland |
| 2001-2002 | Director, Molecular Targets Development Program, Center for Cancer Research (CCR), NCI, Bethesda, Maryland |
| 2002-date | Abraham A. Mitchell Chair and Director, USA Mitchell Cancer Institute; Professor of Medicine & Pharmacology; University of South Alabama, College of Medicine, Mobile, Alabama |

COMMITTEE/ACADEMIC AND OTHER PROFESSIONAL APPOINTMENTS (Selected Listing):

Member, Scientific Advisory Panel, Chemical Industry Institute of Toxicology, 1980-1984

Member, Promotion/Tenure Review Committee, Division of Cancer Treatment, NCI, 1982-1987

Chairman, Decision Network Committee, Division of Cancer Treatment, NCI, 1984-1988 (Member, 1981-1990)

Chairman, Operating Committee, Division of Cancer Treatment, NCI, 1984-1990

Chairman, Biological Evaluation Committee, Division of Cancer Treatment, NCI, 1986-1990

Chairman, Natural Products Research Committee, Division of Cancer Treatment, NCI, 1984-1996

Member, Commissioned Officers Promotion Review Board, United States Public Health Service, 1991-92

Preceptor, Pharmacology/Toxicology Research Associate (PRAT) Program, National Institute of General Medical Sciences, NIH, 1982-2002

Consultant and Grant Reviewer for the Arizona Disease Control Research Commission, State of Arizona, Phoenix, Arizona, 1990-present

Principal Collaborative Investigator, Indo-U.S. Agreement, U.S. National Institute of Mental Health, NIH, National Institute of Mental Health and Neurosciences, Bangalore, India, and National Brain Research Centre, New Delhi, India, 1992-Present

Member,Trans-NIH Microbicides Working Group, Office of AIDS Research, Office of the Director, NIH, 2001-2002

Member, Molecular Targets Faculty, CCR, NCI, 2001-2002

Member, Steering Committee for Molecular Targets Drug Discovery Program, CCR, NCI, 2001-2002

Member, Molecular Targets Executive Committee, CCR, NCI, 2001-2002

Member, University Long-Range Planning Committee, University of South Alabama (USA), 2002-present

Member, Executive Council, USA College of Medicine, 2002-present

Member, Committee on Standards in the Conduct of Research, USA College of Medicine, 2002-present

Member, Patent Committee, USA College of Medicine, 2002-present

Member, USA Research and Technology Corporation Advisory Committee, 2002-present

Ad Hoc Reviewer, Board of Scientific Counselors, National Institute on Aging, NIH, 2002

EDITORIAL DUTIES (Selected Listing):

Member, Editorial Board, The Journal of Antibiotics, Japan Antibiotics Research Association, 2002-present

Member, Commentaries Editorial Advisory Board, Biochemical Pharmacology, Elsevier Press, 1996-present

Member, Editorial Board, Biochemical Pharmacology, Elsevier Press, 1982-1996

Associate Editor, Journal of the National Cancer Institute, U.S. Department of Health and Human Services, 1984-1991

Member, Editorial Board, Fundamental and Applied Toxicology, Society of Toxicology, 1981-1983

Member, Editorial Board, Toxicology and Applied Pharmacology, Academic Press, 1981-1983

Member, Editorial Board, Experimental Lung Research, Elsevier Press, 1980-1983

Member, Editorial Board, Toxicology, Elsevier Press, 1980-1983

MILITARY SERVICE:

U.S. Public Health Service, Commissioned Officer, 1974-2001; Medical Director (Captain, 0-6), 1984-2001; PHS Ser.#42348; Retired, March 1, 2001.

PROFESSIONAL SOCIETIES:

Society of Toxicology
American Chemical Society
American Society of Pharmacognosy
American Association for Cancer Research
American Association for the Advancement of Science
American Society for Pharmacology and Experimental Therapeutics
American Society for Clinical Investigation

HONORS AND AWARDS:

Oswald (President's) Award for Undergraduate Research, University of Kentucky, 1969

Borden Research Prize in Medical Nutrition, Vanderbilt University, 1971

Vanderbilt Vivian Allen M.D.-Ph.D. Fellowship Award, Vanderbilt University, 1971-1975

The Achievement Award of the Society of Toxicology, 1979

The Commendation Medal, U.S. Public Health Service, 1979

Pfizer Award in Clinical Pharmacology, 1987

Pfizer Award in Pharmacology, 1988

The Meritorious Service Medal, U.S. Public Health Service, 1989

The Harold Lupiloff Award for Excellence in Clinical Oncology, 22nd Annual Detroit Cancer Symposium on Anticancer Drug Discovery and Development, 1990

Technology Transfer Awards, U.S. National Cancer Institute, 1993, 1994, 2001.

Recognized by the U.S. Patent & Trademark Office as among the top 400 (above 99$^{th}$ percentile) inventors named on U.S. Patents since 1976.

RESEARCH INTERESTS:

Clinical pharmacology and therapeutics; anticancer and antimicrobial drug discovery and drug development; chemistry and bioactivity of natural products; in vitro and in vivo anticancer and AIDS-antiviral model development; high-throughput screening technologies; metabolism, molecular toxicology and experimental therapeutics of anticancer and anti-HIV agents; extrahepatic mechanisms of xenobiotic metabolism, toxicity and carcinogenesis; pathogenesis and therapy of lung cancer; prostanoid biosynthesis and metabolism in neoplasia

LECTURES PRESENTED AT MAJOR SYMPOSIA (Selected Listing):

Invited lecture, Symposium on "Target Organ Toxicity: Lung," September 16-17, 1975, Cincinnati, Ohio

Invited lecture, Gordon Conference on Drug Metabolism, July 10-15, 1977, Plymouth, New Hampshire

Invited lecture, Symposium on "Clinical Biochemical Pharmacology of 5-Fluorouracil and Anticancer Pyrimidines" July 22-23, 1978, Marseille, France

Invited lecture, International Symposium of the Princess Takamatsu Cancer Research Fund on "Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis", January 23-25, 1979, Tokyo, Japan

Invited lecture, Symposium on "The Scientific Basis of Toxicity Assessment", April 15-19, 1979, Gatlinburg, Tennessee

Invited lecture, Symposium on "Environmental Toxicology", January 19,1979, Burlington, Vermont

Invited lecture, Ciba Foundation Symposium on "The Toxicological Significance of Interaction of Environmental Chemicals with Drug-Metabolizing Enzymes", October 23-25, 1979, London, England

Invited lecture, The Ninth Annual Meeting of the New England Pharmacology Society, January 25-26, 1980, Storrs, Connecticut

Invited lecture, ACS Symposium on "The Pesticide Chemist and Modern Toxicology", June 26, 1980, Dowington, Pennsylvania

Invited lecture, Second International Symposium on "Biological Reactive Intermediates", July 14-17, 1980, Guildford, United Kingdom

Invited participant, Interagency Task Force on Environmental Cancer, Heart, and Lung Disease, Workshop on "Exposure, Metabolism and Mechanisms of Toxicity", January 27-30, 1981, Rockville, Maryland

Invited lecture, International Symposium on "Chemical Indices and Mechanisms of Organ-Directed Toxicity", March 4-7, 1981, Barcelona, Spain

Invited lecture and co-chairman, Symposium on "Nonrespiratory Metabolic Functions of the Lung", Annual Meeting of the Federation of American Societies for Experimental Biology, April 12-17, 1981, Atlanta, Georgia

Invited lecture, Symposium on "Biological Kinetics of Chemically Reactive Metabolites", November 1-6, 1981, Sarasota, Florida

Keynote address, Symposium on "Metabolite-Mediated Toxicity", 15th Annual Meeting of the Australasian Society of Clinical and Experimental Pharmacologists, December 14-16, 1981, Adelaide, South Australia

Invited lecture, Symposium on "Toxicity Testing; New Approaches and Applications in Human Risk Assessment", September 14-15, 1983, St. Louis, Missouri

Invited lecture, International Meeting on "Chemical Carcinogenesis II, Xenobiotics and Biotransformation", October 12-15, 1983, Sasari, Italy

Invited speaker, General Motors Conference on "Cancer Therapy, Where Do We Go From Here", September 14-15, 1984, Jackson Hole, Wyoming

Chairman and speaker, NCI Workshop on "Disease-oriented Antitumor Drug Discovery and Development", January 9-10, 1985, Bethesda, Maryland

Invited speaker, US-Japan Joint Seminar, February 25-26, 1985, Oahu, Hawaii

Invited lecture, 4th World Conference on Lung Cancer, August 25-30, 1985, Toronto, Canada

Invited lecture, International Union Against Cancer (UICC) - Study Group Meeting, September 9-11, 1985, Oslo, Norway

Invited lecture and co-chairman, FASEB Summer Conference on "Lung Pharmacology", July 28-August 1, 1986, Saxton's River, Vermont

Invited speaker, First Beijing International Symposium on "Cancer Treatment and New Trends of Cancer Chemotherapy", September 7-9, 1986, Beijing, China

Invited lecture, Fifth NCI/EORTC Symposium on "New Drugs in Cancer Therapy", October 22-24, 1986, Amsterdam, The Netherlands

Chairman and speaker, NCI/NIAID Workshop on "Issues for Implementation of a National Anti-HIV Preclinical Drug Evaluation Program; Critical Parameters for an In Vitro, Human Host-cell Based, Primary Screen",April 8-9, 1987, Rockville, Maryland

Pfizer Lecture in Clinical Pharmacology, University of Mississippi Medical Center, May 18-19, 1987, Jackson, Mississippi

Chairman and speaker, NCI Workshop, "Issues Concerning Selection, Characterization and Quality Control of Human Tumor Cell-Lines for the National Cancer Institute's New Drug Screening Program", May 27-28, 1987, Bethesda, Maryland

Invited lecture, EORTC Pharmacokinetics and Metabolism (PAM) Group Symposium, June 18, 1987, Lyon, France

Invited lecture, Workshop of the EORTC New Drug Development and Coordinating Committee (NDDCC), June 19, 1987, Lyon, France

Invited lecture, 57th ANZAAS Congress, James Cook University of North Queensland, August 28, 1987, Townsville, Australia

Pfizer Lecture in Pharmacology, Texas Tech University School of Medicine, May, 1988, Lubbock, Texas

Invited lecture, Society of Toxicology Symposium on "AIDS Drug Development and Toxicology", March 2, 1989, Atlanta, Georgia

Invited lecture, Sixth NCI EORTC Symposium, on "New Drugs in Cancer Therapy", March 7-10, 1989, Amsterdam, The Netherlands

Invited lecture, US-Japan Cooperative Cancer Research Program, Seminar on "Marine Natural Products and Cancer", March 23-24, 1989, Oahu, Hawaii

Invited lecture, Japanese Foundation for Cancer Research Symposium on "Cancer Chemotherapy", April 19-21, 1989, Tokyo, Japan

Invited lecture, American Association for Cancer Research Symposium on "Prediction of Tumor Response", May 25, 1989, San Francisco, California

Keynote address, 20th Symposium on "Drug Metabolism and Drug Action and Toxicity", October 12-13, 1989, Sapporo, Japan

Invited lecture, Phase I-II Study Group of the Medical Association of International Medicine, November 23-24, 1989, Frankfurt, Germany

Invited lecture, Twenty-Second Annual Cancer Symposium on "Anticancer Drug Discovery and Development", April 26-28, 1990, Detroit, Michigan

Invited lecture, Gordon Conference on "Marine Natural Products", February 17-21, 1992, Ventura, California

Invited participant, National Heart, Lung and Blood Institute Working Group on "Pulmonary Complications Associated with Breast Cancer Therapy", September 20, 1993, Rockville, Maryland

Invited participant, International Conference on "Oxidative Stress in HIV Disease", November 8-10, 1993, NIH, Bethesda, Maryland

Invited lecture, Symposium on "Intellectual Property Rights for Naturally Derived Bioactive Compounds and the Conservation of Biodiversity", October 21-24, 1994, San Jose, Costa Rica

Invited participant, Symposium on "Anti-HIV Microbicides", NIAID/WHO, May 19-20, 1998, Atlanta, Georgia

Plenary lecture, 9th International Symposium on "Marine Natural Products", July 5-10, 1998, Townsville, Australia

Invited lecture, Symposium on "Advances in Transfusion Safety", March 18-20, 1999, San Francisco, California

Invited speaker, Alliance for Microbicide Development, May 10-11, 1999, Washington, D.C.

Invited lecture, Symposium on "New Prospects in Anticancer Agents", American Chemical Society National Meeting, March 26-31, 2000, San Francisco, California.

Dedication Address, ASU Cancer Research Institute, Arizona State University, March 6, 2001, Tempe, Arizona.

Invited lecture, NIAID Collaborative Antiviral Testing Group (CATG) Annual Meeting, National Institute of Allergy and Infectious Diseases, NIH, May 9-10, 2001, Bethesda, Maryland.

Invited participant, NIH Office of AIDS Research (OAR) Planning Workshop on Microbicides Research, February 6, 2002, Washington, D.C.

Invited lecture, UICC International Cancer Congress, June 30-July 5, 2002, Oslo, Norway.

Invited lecture, "The NCI Developmental Therapeutics Program 50th Anniversary Symposium, NCI, NIH, Bethesda, Maryland, November 29, 2005.

CURRENT GRANT & CONTRACT FUNDING (Principal Investigator):

DOE DE-FG02-02CH11115, USA-CRI Construction & Equipment, 09/30/02- 06/30/06, $6,761,000.

DOE DE-FG02-02CH1115-A002, USA-CRI Equipment, 9/30/02-06/30/06, $241,000.

HRSA 1C76HF00562-01, Health Care Facility, 9/30/02-09/15/06, $3,732,450.

HRSA 1C76HF0118-01, Health Care Facility & Equipment, 09/01/03-01/31/06, $19,641,298.

PRESENT ADDRESS:

Residence:
109 Austill Avenue
Mobile, Alabama 36608

Office:
MSB 2015
College of Medicine
University of South Alabama
Mobile, Alabama 36688-0002

PATENTS AND PATENTS PENDING:

Boyd, M.R., Cardellina, J.H., Gustafson, K.R., McMahon, J., Weislow, O.S., Shoemaker, R.H., Paull, K.D.: Antiviral Compositions Containing Sulfoquinovosyl Glycerol. Derivatives and Analogs Thereof and Methods for Using. Japanese Patent No. 2022435, issued May 24,1995; Australian Patent No. 635057, issued July 5, 1993.

Vistica, D.T., Scudiero, D.A., Monks, A.P., Skehan, P.J., Boyd, M.R.: $CO_2$-Independent Growth Medium for Maintenance and Propagation of Cells. Australian Patent No. 653927, issued February 15, 1995; Japanese Patent No. 2074371, issued July 25,1996; European Patent No. 0512066, issued November 13, 1996.

Boyd, M.R., Cox, P.A., Cragg, G.M., Blumberg, P.M., Sharkey, N.A., Ishitoya, J., McMahon, J.B., Beutler, J.A., Weislow, O.S., Cardellina, J.H., Gustafson, K.R.: Antiviral Composition. Japanese Patent No. 2020302, issued February 19, 1996; Australian Patent No. 639343, issued November 12, 1993; Canadian Patent No. 2,083,945, issued February 7, 1995; European Patent No. 0531413, issued August 28, 1998; U.S. Patent No. 5,599,839, issued February 4, 1997.

Boyd, M.R., Cardellina, J.H., Manfredi, K.P., McMahon, J.B., Blunt, J.W., Pannell, L.K., Cragg, G.M., Jato, J.: Michellamine Antiviral Agents, Composition and Treatment Methods. Japanese Patent No. 1957368, issued August 10, 1995; Australian Patent No. 657549, issued July 4, 1995; Canadian Patent No. 2,100,066, issued August 13, 1996; European Patent No. 0594795, issued December 18, 2002; U.S. Patent No. 5,455,251, issued October 3, 1995.

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., McMahon, J.B., Fuller, R.W., Cragg, G.M., Kashman, Y.: Calanolide Antiviral Compounds; Compositions and Use. European Patent No. 0633887, issued May 19, 1999; Japanese Patent No. 3103114, issued August 20, 2000.

Boyd, M.R., Cardellina, J.H. II, Fuller, R.W., Snader, K.M., Clardy, J.: Novel Antitumor Compound, Compositions and Method of Use. Australian Patent No. 657614, issued August 15, 1995; U.S. Patent No. 5,283,383, issued February 1, 1994.

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., Decosterd, L., Parsons, I.C., Pannell, L.K., McMahon, J.B., Cragg, G.M.: Antiviral Naphthoquinone Compounds, Compositions and Uses Thereof. European Patent No. 0681578, issued July 5, 1997; Australian Patent No. 680872, issued December 4, 1997; Japanese Patent No. 2922648, issued April 30, 1999; Canadian Patent No. 2,155,020, issued July 13, 2004; U.S. Patent No. 5,672,607, issued September 30, 1997.

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., McMahon, J.B., Fuller, R.W., Cragg, G.M., Kashman, Y., Soejarto, D.: Calanolides and Related Antiviral Compounds, Compositions and Uses Thereof. Japanese Patent No. 2852706, issued November 20, 1998; Australian Patent No. 685468, issued January 22, 1998; European Patent No. 0699202, issued March 3, 1999; Canadian Patent No. 2,163,348, issued February 1, 2000; U.S. Patent No. 5,591,770, issued January 7, 1997.

Boyd, M.R., François, G., Bringmann, G., Hallock, Y., Manfredi, K., Cardellina, J.H. II: Antimalarial Korupensamines and Pharmaceutical Compositions and Medical Uses Thereof. Canadian Patent No. 2,183,247, issued August 17, 1999; Australian Patent No. 690640, issued September 10, 1998; U.S. Patent No. 5,409,938, issued April 25, 1995.

François, G., Bringmann, G., Phillipson, J.D., Boyd, M.R., Timperman, G., Schneider, C., Ake Assi, L.: Antimalarial Naphthylisoquinoline Alkaloids and Pharmaceutical Compositions and Medical Use Thereof. Australian Patent No. 690967, issued November 5, 1998; Canadian Patent No. 2,183,155, issued September 9, 2003; U.S. Patent No. 5,639,761, issued June 17, 1997.

Bringmann, G., Götz, R., Boyd, M.R.: Monomeric Naphthylisoquinoline Alkaloids and Synthesis Methods Thereof. Australian Patent No. 709428, issued August 26, 1999. U.S. Patent No. 5,552,550, issued September 3, 1996.

Bringmann, G., Harmsen, S., Boyd, M.R.: Dimeric Naphthylisoquinoline Alkaoids and Synthesis Methods Thereof. U.S. Patent No. 5,571,919, issued November 5, 1996.

Bringmann, G., Harmsen, S., Gotz, R., Boyd, M.R.: Monomeric and Dimeric Naphthylisoquinoline Alkaloids and Synthesis Methods Thereof. European Patent No. EP0772595B1, February 4, 2003.

Bringmann, G.R., Boyd, M.R., Gotz, R., Kelly, T.R.: Dimeric Arylisoquinoline Alkaloids and Synthesis Methods Thereof. Australian Patent No. 699121, issued March 11, 1999; U.S. Patent No. 5,578,729, issued November 26, 1996.

Boyd, M.R., Gustafson, K.R., McMahon, J.B., Shoemaker, R.H.: Antiviral Proteins and Peptides. Australian Patent No. 707781 issued November 4, 1999; Australian Patent No. 746809, issued August 15, 2002; European Patent No. 0836647, issued April 21, 2004; U.S. Patent No. 5,843,882, issued December 1, 1998.

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., Decosterd, L., Parsons, I.C., Pannell, L.K., McMahon, J.B., Cragg, G.M.: Antiviral Naphthoquinone Compounds, Compositions and Uses Thereof. U.S. Patent No. 5,869,522, issued February 9, 1999.

Boyd, M.R., Cardellina, J.H. II, Manfredi, K.P., Blunt, J.W., Pannell, L.K., McMahon, J.B., Gulakowski, R.J., Cragg, G.M., Bringmann, G., Thomas, D., Jato, J.: Process of Preparing Michellamine Compounds. U.S. Patent No. 5,654,432, issued August 5, 1997.

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., Decosterd, L., Parsons, I.C., Pannell, L.K., McMahon, J.B., Cragg, G.M.: Antiretroviral Naphthoquinone Compounds, Compositions and Uses Thereof. U.S. Patent No. 5,783,598, issued July 21, 1998.

Boyd, M.R., Gustafson, K.R., McMahon, J.B., Shoemaker, R.H.: Nucleic Acids Encoding Antiviral Proteins and Peptides, Vectors and Host Cells Comprising Same, & Methods of Producing the Antiviral Proteins and Peptides. U.S. Patent No. 5,821,081, issued October 13, 1998.

Boyd, M.R., Cardellina, J.H. II, Gustafson, K.R., McMahon, J.B., Fuller, R.W., Cragg, G.M., Kashman, Y., Soejarto, D.: Calanolides and Related Antiviral Compounds, Compositions and Uses Thereof. U.S. Patent No. 5,859,049, issued January 12, 1999.

Bringmann, G., Götz, R., Boyd, M.R.: Monomeric Naphthylisoquinoline Alkaloids and Synthesis Methods Thereof. U.S. Patent No. 5,763,613, issued June 9, 1998.

Bringmann, G., Harmsen, S., Boyd, M.R.: Dimeric Naphthylisoquinoline Alkaloids and Synthesis Methods Thereof. U.S. Patent No. 5,789,594, issued August 4, 1998.

Bringmann, G., Boyd, M.R., Götz, R., Kelley, T.R.: Dimeric Arylisoquinoline Alkaloids and Synthesis Methods Thereof. U.S. Patent No. 5,786,482, issued July 28, 1998.

Boyd, M.R., McMahon, J.B.: An Anti-Cyanovirin Antibody. U.S. Patent No 5,998,587, issued December 7, 1999.

Boyd, M.R., Gustafson, K.R.: Methods of Obtaining Antiviral Proteins and Antiviral Peptides from Nostoc Ellipsosporum. U.S. Patent No. 5,962,653, issued October 5, 1999.

Boyd, M.R., Shoemaker, R.H.: Nucleic Acids Encoding Antiviral Proteins and Peptides Fused to Effector Proteins. U.S. Patent No. 5,962,668, issued October 5, 1999.

Boyd, M.R.: Method of Using Cyanovirins. U.S. Patent No. 6,015,876, issued January 18, 2000.

François, G., Bringmann, G., Phillipson, J.D., Boyd, M.R., Timperman, G., Schneider, C., Ake Assi, L.: Naphthylisoquinoline Alkaloids, Pharmaceutical Compositions Containing Them and Their Use for the Treatment of Malaria. European Patent No. 0741569, issued April 27, 2005; U.S. Patent No. 6,627,641, issued September 30, 2003.

Boyd, M.R., McKee, T.C., Cardellina, J.H. II, Beutler, J.A., Erickson, K., Galinis, D., Pannell, L.: Macrocyclic Lactones, Compositions and Methods of Use. PCT International Patent Application No. PCT/US98/15011, July 23, 1998; European Patent Application No. 98935844.5; Canadian Patent Application No. 2,297,198; International Publication No. WO 99/05136; European Patent Bulletin Publication No. 1000053; Japanese Patent No. 510838/2001, issued August 7, 2001; Australian Patent No. 740668, issued February 21, 2002; U.S. Patent No. 6,353,019B1, issued March 5, 2002.

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Bringmann, G., Boyd, M.R., Wenzel, M.: Monomeric and Dimeric Arylisoquinoline Alkaloids and Derivatives Thereof. PCT International Patent Application No. PCT/US98/27407, December 23, 1998; International Publication No. WO96/34107, July 8, 1999; Australian Patent No. 751591, issued December 12, 2002; U.S. Patent No. 6,140,339, issued October 31, 2000.

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# Identification of a New Chondropsin Class of Antitumor Compound That Selectively Inhibits V-ATPases*

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**Emma Jean Bowman‡§, Kirk R. Gustafson¶, Barry J. Bowman‡, and Michael R. Boyd‖**

*From the ‡Department of Molecular, Cell, and Developmental Biology, University of California, Santa Cruz, California 95064, the ¶Molecular Targets Development Program, Center for Cancer Research, NCI, National Institutes of Health, Frederick, Maryland 21702, and ‖USA Cancer Research Institute, University of South Alabama, Mobile, Alabama 36688*

**We identify a new naturally occurring class of inhibitor of vacuolar $H^+$-ATPases (V-ATPases) isolated from vacuolar membranes of *Neurospora crassa* and from chromaffin granule membranes of *Bos taurus*. To date, the new class includes six chondropsins and poecillastrin A, large polyketide-derived macrolide lactams with 33–37 membered rings. In the National Cancer Institute's 60-cell screen the chondropsin class showed a tumor cell growth inhibitory fingerprint essentially indistinguishable from that of the bafilomycin/concanamycin and the salicylihalamide/lobatamide classes of well-established V-ATPase inhibitors. Half-maximal inhibition of V-ATPase activity *in vitro* occurred at 0.04–0.7 μM for the fungal vacuolar V-ATPase and at 0.4 to >10 μM for the chromaffin granule V-ATPase. Thus, the new inhibitors are somewhat less potent than the other two classes, which typically have $K_i$ values of <10 nM for V-ATPases, and the new inhibitors differ from the other two classes in their specificity. The bafilomycin class inhibits all eucaryotic V-ATPases, the salicylihalamide class inhibits mammalian V-ATPases but not fungal V-ATPases, and the new chondropsin class inhibits the *N. crassa* V-ATPase better than the chromaffin granule V-ATPase. Two mutations in the *N. crassa* V-ATPase that affect the binding of bafilomycin had small but reproducible effects on the affinity of chondropsins for the V-ATPase, suggesting the possibility of a similar mechanism of inhibition.**

Two classes of natural products act as specific and potent inhibitors of vacuolar $H^+$-ATPases (V-ATPases)[1] (Fig. 1). The macrocyclic lactones, bafilomycin and concanamycin, were identified as inhibitors of eucaryotic V-ATPases from animals, plants, and fungi (1, 2). Subsequently tested in the National Cancer Institute's (NCI) 60-cell antitumor screen, they showed a characteristic tumor cell growth inhibitory profile, particularly potent against melanoma cell lines. More recently, a large class of benzolactone enamides, including salicylihalamides and lobatamides, produced an inhibitory profile in the 60-cell screen nearly identical to that for bafilomycin/concanamycin. Subsequent analysis showed them to be excellent V-ATPase inhibitors. Surprisingly, this class preferentially inhibited V-ATPases from mammalian sources, with little effectiveness against V-ATPases from *Neurospora crassa* and *Saccharomyces cerevisiae* (3).

V-ATPases are abundant, ubiquitous ion pumps in eucaryotic cells (reviewed in Ref. 4). They regulate pH and generate an electrochemical gradient that drives the transport of molecules across many types of cellular membranes. A diverse collection of physiological processes depend on V-ATPases, including protein sorting, endocytosis, neurotransmitter uptake, apoptosis, and receptor recycling. The V-ATPase is a large, complex enzyme. The membrane-embedded sector, Vo, contains at least five different polypeptides (a, c, c′, c″, and d) and forms a proton-conducting pathway through the membrane. The peripheral sector, V1, is composed of at least eight different polypeptides (A–H) and contains the sites of ATP hydrolysis. Like the F-ATPase in mitochondria, chloroplasts, and bacteria (5), the V-ATPase functions as a molecular motor (6–8). The A and B subunits provide the driving force by hydrolysis of ATP. The D, F, c, c′, and c″ subunits are tightly bound to each other and form the rotor. Other subunits, a, G, and H, form a stator, anchoring the A and B subunits to the membrane. The translocation of protons has been proposed to occur at the interface between the rotating ring of c subunits and the fixed a subunit (9).

Not surprisingly, given their widespread occurrence and involvement with so many cellular processes, V-ATPases play a role in many diseases, *e.g.* Alzheimer's, osteoporosis, viral infections, diabetes, cardiovascular disorders, and cancer (4, 10–12). They are also implicated in tumor growth and resistance to anticancer agents (13–16). Because of the potential of V-ATPases as lead compounds to therapeutic drugs, several laboratories have undertaken and achieved the complete *in vitro* synthesis of bafilomycin, concanamycin, salicylihalamide, and lobatamide (17–22). Derivatives of bafilomycin have been generated and tested for effects on osteoporosis in rats; one gave encouraging results in preventing bone loss in ovariectomized animals (23).

In this report we introduce the chondropsins as a third class of natural products that exhibit the same NCI 60-cell antitumor fingerprint as bafilomycin, salicylihalamide, and related compounds and selectively inhibit V-ATPase activity *in vitro*. We use mutants from *N. crassa* that are resistant to bafilomycin to ask whether the new class of V-ATPase inhibitor may interact with the enzyme in a manner similar to the established inhibitors (24).

## EXPERIMENTAL PROCEDURES

*N. crassa Strains, Growth of Cells*—Strain 74A of *N. crassa* was used as the wild type. The mutant strains, bfr33 and bfr65, were described previously (24). Briefly, they carry mutations in *vma-3*, the gene encoding subunit c of the V-ATPase, that allow them to grow in the presence of bafilomycin at alkaline pH and confer resistance to bafilomycin on

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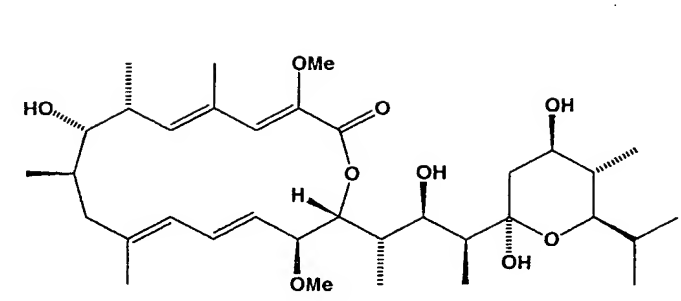
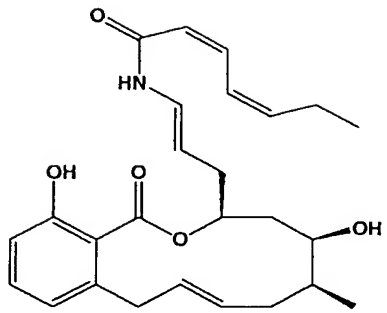
§ To whom correspondence should be addressed: Dept. of Molecular, Cell, and Developmental Biology, University of California, Santa Cruz, CA 95064. Tel.: 831-459-3448; Fax: 831-459-3139; E-mail: rbowman@biology.ucsc.edu.

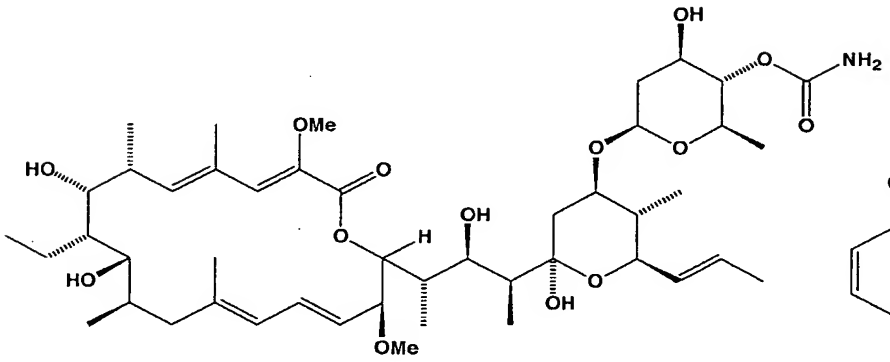
[1] The abbreviations used are: V-ATPase, vacuolar $H^+$-ATPase; F-ATPase, $F_1F_o$ ATP synthase; NCI, National Cancer Institute.



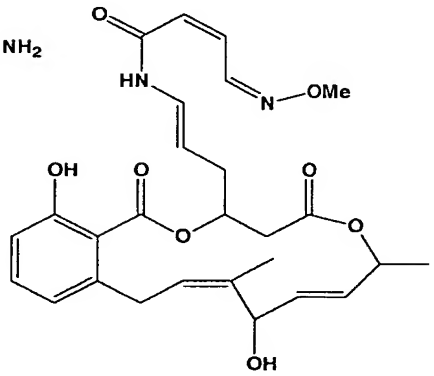

bafilomycin $A_1$




salicylihalamide A




concanamycin A




lobatamide A

FIG. 1. **Structures of bafilomycin A1, salicylihalamide A, concanamycin A, and lobatamide A.**

the V-ATPase *in vitro*. The altered residues in subunit c are T32I and Y143H for strains bfr33 and bfr65, respectively. The strains are available at the Fungal Genetics Stock Center, Kansas City, KA. Strains were maintained on Vogel's medium N (a minimal medium salt solution at pH 5.8) supplemented with 2% sucrose. For membrane isolations, cells were grown ~14 h at 25 °C in 4 liters of Vogel's medium inoculated with $10^6$ conidia/ml (asexual spores) and aerated vigorously.

*Isolation of Membranes, Analysis of ATPase Activity, and Effects of Inhibitors*—Chromaffin granule membranes were prepared from bovine adrenal glands, obtained fresh from a local abattoir, as described (25). The membranes were stored in aliquots at −70 °C. Vacuolar membranes, mitochondria, and plasma membranes were prepared from *N. crassa* as described (26) and modified (27). Protein and ATPase activities were assayed as described (26), except that assays were typically done at 37 °C. The chondropsins and poecillastrin A were added to assay mixtures from 5 or 10 mM stock solutions in dimethyl sulfoxide. When comparing the effects of inhibitors on different membranes, we ran the reactions at the same time in the same assay mix.

*Compounds*—The macrolide lactams used in this work are illustrated in Fig. 2. They were isolated and purified from various marine sponges at the National Cancer Institute. Chondropsins A, B, and D were isolated from *Chondropsin* sp (28, 29) chondropsin C and 73-deoxychondropsin A, from *Ircina* sp (30) and poecillastrin A, from *Poecillastra* sp (31). Dimethylchondropsin A was obtained by methylation of chondropsin A as described (28). All seven compounds were tested for their effects on V-ATPase activity in bovine chromaffin granule membranes and *N. crassa* vacuolar membranes. Chondropsin B and 73-deoxychondropsin A were chosen for studies on inhibitor effects on other ATPases and on V-ATPases in mutant strains because they were available in larger quantities.

*Testing of Compounds in the NCI 60-Cell Screen*—Compounds were tested in the NCI 60-cell screen (32) as described previously (33) in at least quadruplicate in each of two different concentration ranges ($10^{-6}$ and $10^{-7}$ M upper limits) using five, 1 $\log_{10}$-spaced dilutions against the full 60-cell panel. Average-mean graphs were prepared from the appropriate data for each compound, and COMPARE correlation analyses were performed as described previously (33).

*Materials*—Concanamycin C was a gift from Dr. K. Altendorf (University of Osnabrück) and Dr. A. Zeeck (University of Göttingen). The $Na^+/K^+$ ATPase from dog kidney, ATP, sorbitol, phenylmethylsulfonyl fluoride, chymostatin, and most other chemicals were purchased from Sigma.

## RESULTS

*COMPARE Analyses Implicate V-ATPase as a Molecular Target of the Chondropsins*—We used the NCI 60-cell antitumor screen to look for biological activity of the chondropsins similar to compounds in the NCI databases (33). A dose-response curve was determined for each type of tumor cell, measuring cytotoxicity in microtiter plates after a 48-h exposure to the test compound. The most sensitive cell lines were killed at concentrations that were nearly 10,000-fold lower than the concentrations that affected the most resistant types of cells. Each cell line was compared with the mean effective dose for all cell lines, generating a "mean graph" that served as a profile of the response of the 60 cell lines to each test compound. This cellular response profile was compared with the response profiles of other test compounds using the COMPARE pattern recognition algorithm (33). We found that the 60-cell profiles of chondropsin A gave consistently high correlation with the data base profiles of lobatamide A, bafilomycin A1, salicylihalamide A, and concanamycin A (Table I). Because these four compounds are potent specific inhibitors of V-ATPases, this result prompted us to hypothesize that the new class of macrolide lactams might also target V-ATPases.

*Chondropsins and Poecillastrin A Inhibit V-ATPases*—The six chondropsins and poecillastrin A (see structures in Fig. 2) were tested for their effect on V-ATPases from bovine chromaffin granule membranes and from vacuolar membranes of

TABLE I
*Chondropsin A gives similar results to V-ATPase inhibitors in the NCI in vitro screen*

| Compound | TGI-COMPARE correlation coefficient | Mean-Panel $GI_{50}$ |
|---|---|---|
| | | $\times 10^{-8}$ M (±S.D.) |
| Lobatamide A | 1.00 | 0.56 (0.09) |
| Concanamycin A | 0.94 | 0.11 (0.03) |
| Bafilomycin $A_1$ | 0.92 | 1.02 (0.71) |
| Salicylihalamide A | 0.93 | 4.97 (1.03) |
| Chondropsin A | 0.92 | 2.56 (0.77) |

*N. crassa*. As predicted, they inhibited V-ATPase activity *in vitro*. However, the specificity of their inhibition was different from that of either the bafilomycin/concanamycin class or the salicylihalamide/lobatamide class. Bafilomycin and its relatives act against all eucaryotic V-ATPases that have been tested (34). The salicylihalamide class shows a clear preference for V-ATPases from mammalian sources and is ineffective toward V-ATPases from fungi (3). To our knowledge, all animal V-ATPases tested to date are sensitive to this class of compounds.

By contrast, the new class of macrolide lactams inhibited V-ATPases from both bovine chromaffin granules and fungal vacuoles but was more potent against the fungal enzyme. For example, half-maximal inhibition of the chromaffin granule V-ATPase by chondropsin B and 73-deoxychondropsin A occurred at 5.8 and 2.9 μM, respectively, and half-maximal inhibition of the *N. crassa* V-ATPase by the same compounds was at 0.27 and 0.10 μM (Fig. 3, *A* and *B*). Data for effects of the seven macrolide lactams on the two V-ATPases are summarized in Table II. They showed a consistent pattern. All seven compounds were more potent inhibitors (8–30-fold) of the enzyme from *N. crassa* than the enzyme from the animal. The order of potency was similar for the two enzymes. Dimethylchondropsin A and chondropsin D were the strongest inhibitors, followed by chondropsin C and 73-deoxychondropsin A, and then poecillastrin A and chondropsin B; chondropsin A was the weakest inhibitor in this group.

The concentrations for half-maximal inhibition by the chondropsins ranged from 0.04 to 0.7 μM for the fungal enzyme and from 0.43 to >10 μM for the mammalian enzyme. Thus, although good inhibitors, they were not as potent as the previously characterized V-ATPase inhibitors, which typically have $K_i$ values of 5 nM or less against their target enzymes when assayed *in vitro* (1–3). The relatively weak activity of chondropsin A against the chromaffin granule V-ATPase was unexpected. In the NCI 60-cell screen chondropsin A was ~2-fold more potent an inhibitor of tumor cell growth than salicylihalamide A (Table I), which inhibits the chromaffin granule enzyme *in vitro* with a $K_i$ of 3 nM (data not shown). We speculate that the new class of compounds may target specific isoform(s) of mammalian V-ATPase yet to be defined.

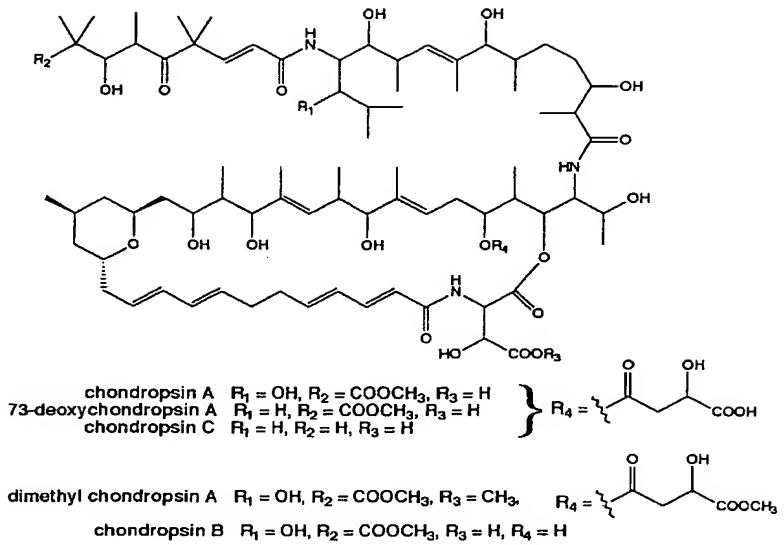
*The Chondropsins and Poecillastrin A Are Inactive Against Other Membrane ATPases*—We previously demonstrated that the macrocyclic lactone and the benzolactone enamide classes of V-ATPase inhibitors do not inhibit F-ATPases from mitochondria or *Escherichia coli* or the plasma membrane $H^+$-ATPase from *N. crassa* (1, 2). High concentrations of bafilomycin and concanamycin do inhibit mammalian P-type ATPases. Bafilomycin C1 inhibited the $Na^+/K^+$ ATPase of dog kidney with a $K_i$ of 13 μM (35), whereas bafilomycin A1 inhibited the dog kidney enzyme with a $K_i$ of 30 μM (1), 10,000 times greater than the $K_i$ for V-ATPase inhibition. In the current study 0.1, 1.0, and 10.0 μM concentrations of chondropsin B and 73-deoxychondropsin A had no effect on the activity of the mitochondrial F-ATPase of *N. crassa*, the plasma membrane $H^+$-ATPase of *N. crassa*, or the $Na^+/K^+$ ATPase from dog kidney (data not shown).

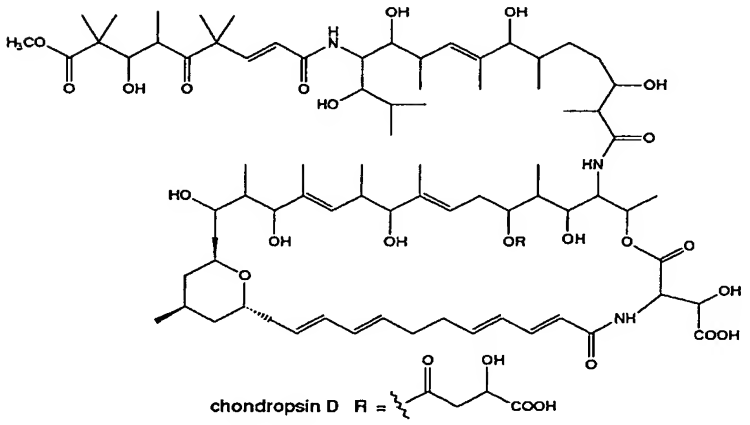
*V-ATPase Mutations That Confer Resistance to Bafilomycin Cause Small but Reproducible Changes in Inhibition by Chondropsins*—We have isolated bafilomycin-resistant mutant strains of *N. crassa* that are altered in subunit c of the V-ATPase. Assayed *in vitro*, the mutant enzymes show 20–60-fold resistance to bafilomycin (24). Three of the mutants consistently exhibited a 3-fold resistance to concanamycin as well. We reasoned that if the chondropsins bind the V-ATPase at the same sites as bafilomycin and concanamycin, they should have a changed affinity for the mutant enzymes as compared with the wild type enzyme. We tested the effects of chondropsin B and 73-deoxychondropsin A on the V-ATPases from the wild type strain 74A and from two mutant strains, bfr33 (T32I) and bfr65 (Y143H). The two chondropsins had similar effects on the mutant enzymes, giving a 2.5-fold increase in $K_i$ for the bfr33 enzyme and a 2-fold decrease in $K_i$ for the bfr65 enzyme as compared with the wild type control (Fig. 4, *A* and *B*, Table III). The experiment was done three times. We assayed two different preparations of vacuolar membranes from each mutant strain and three from the wild type. The increase in $K_i$ for the bfr33 enzyme with the two chondropsins ranged from 2.2–3.3-fold, and the decrease in $K_i$ for the bfr65 enzyme ranged from 1.4–2.3-fold. Thus, although small, the effects were reproducible. These results can be interpreted as suggesting that the chondropsins interact with the V-ATPase in a similar manner to bafilomycin. Alternatively, the small changes in the $K_i$ for chondropsins could be due to indirect effects; a conformational change in subunit c could alter chondropsin binding at another site in the enzyme.

## DISCUSSION

V-ATPases are the target of a variety of antibiotics that have been isolated in screens of natural products. Three classes stand out by their characteristic structures (Figs. 1 and 2). The family of bafilomycins and concanamycins, macrolide antibiotics with 16- or 18-membered lactone rings, comes from *Streptomyces* sp; they inhibited growth of bacteria and fungi in a disc diffusion assay. The first potent specific inhibitors of V-ATPases to be identified, bafilomycin and concanamycin became important aids in characterizing V-ATPases in new locations and in probing the role of V-ATPases in a number of physiological processes (34). The family of salicylihalamides, lobatamides, oximidines, and apicularens are benzolactone enamides described by three structural features, (*a*) a salicylic acid residue, (*b*) an enamide side chain, and (*c*) a linker of variable length, composition, and stereochemistry that joins a and b, forming a lactone ring. Originally isolated from marine sponges and ascidians, these compounds exhibited potent tumor growth inhibition in the NCI 60-cell screen. The cellular response profiles from this screen matched the profiles of bafilomycin and concanamycin in the NCI data base, prompting us to test them for inhibitory activity against V-ATPases. Confirmed as excellent V-ATPase inhibitors, the benzolactone enamide class had the unprecedented property of discriminating between mammalian and fungal V-ATPases (3). They are currently under study by several laboratories as potential therapeutic leads (36).

In this report we identify a third class of natural product as V-ATPase inhibitors. Once again, the class members were isolated from marine sponges and suspected to act as V-ATPase inhibitors because of their distinctive pattern of cellular growth inhibition and cytotoxicity in the NCI 60-cell screen. A mean-graph COMPARE analysis (33) revealed a high correlation between the 60-cell profiles of the chondropsins and the other known inhibitors of V-ATPase (Table I). Compounds that correlate highly with one another can be expected to share a



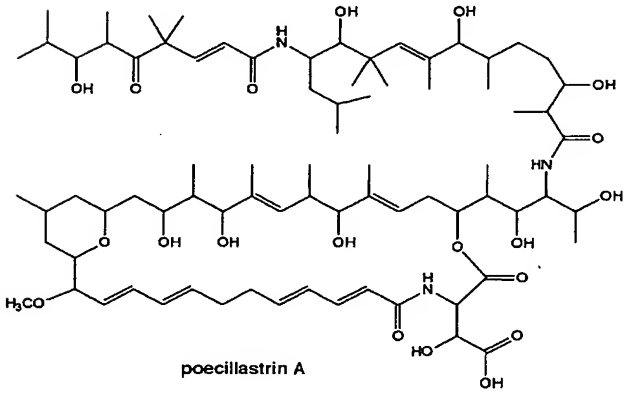




FIG. 2. **Structures of six chondropsins and poecillastrin A.**

common molecular target or biological mechanism of action, even if they differ significantly in structure. The new class, presently composed of six chondropsins and poecillastrin A, are polyketide-derived macrolide lactams with 33–37 members in the macrocyclic ring (Fig. 2) (28–31). The compounds selectively inhibit V-ATPases (Fig. 3, *A* and *B*, Table II) and have no inhibitory activity on membrane ATPases from the F- and P-ATPase families.

The new class of V-ATPase inhibitor differs from the other classes in two ways: it is less potent, and it preferentially

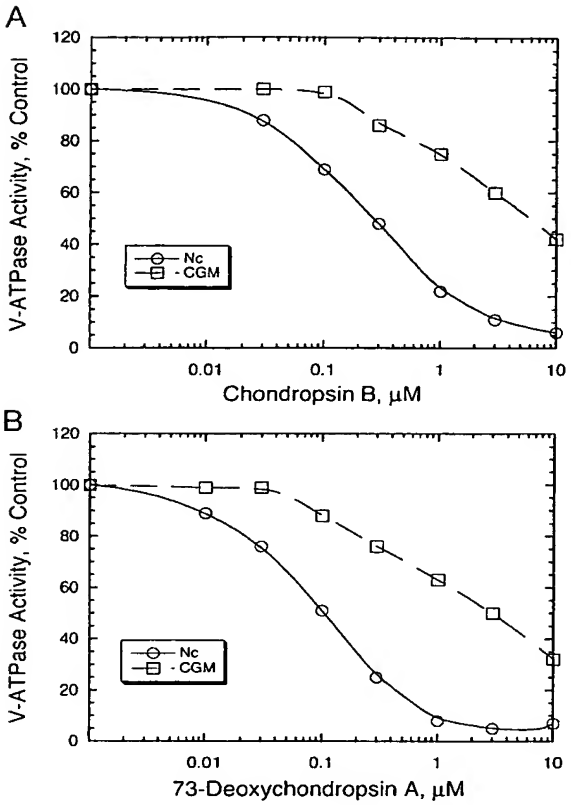



FIG. 3. **The chondropsins differentially inhibit V-ATPases from *N. crassa* vacuoles and bovine chromaffin granules.** The effect of two chondropsins on V-ATPase activity in vacuolar membranes of *N. crassa* (2 μg of protein) and in bovine chromaffin granule membranes (20 μg of protein) was assayed at 37 °C. Specific activities in the absence of inhibitor were 5.0 μmol/min/mg for the *N. crassa* enzyme and 0.18 μmol/min/mg for the bovine enzyme. *A*, half-maximal inhibition by chondropsin B was achieved at 0.27 μM for the fungal V-ATPase and at 5.8 μM for the bovine V-ATPase. *B*, half-maximal inhibition by 73-deoxychondropsin A was achieved at 0.10 μM for the fungal V-ATPase and at 2.9 μM for the bovine V-ATPase.

TABLE II
*Effect of chondropsins on V-ATPase of bovine chromaffin granule membranes and of N. crassa vacuolar membranes*

V-ATPase activities were measured at 37 °C with 20 μg of chromaffin granule membrane protein or 2 μg of vacuolar membrane protein, and concentrations of the six chondropsins and poecillastrin A as illustrated in Fig. 3, *A* and *B*. Specific activities in the absence of inhibitor were 0.18 μmol/min/mg of protein for the chromaffin granule membrane (CGM) V-ATPase and 5.0 μmol/min/mg of protein for the vacuolar membrane (VM) V-ATPase. Each value is the average of three independent titrations. Structures of inhibitors are in Fig. 2.

| | $K_i$ for bovine CGM | $K_i$ for Nc VM | Ratio CGM/VM |
|---|---|---|---|
| | μM | μM | |
| Chondropsin A | >10.0 | 0.70 | >14 |
| Chondropsin B | 6.6 | 0.32 | 21 |
| Chondropsin C | 2.7 | 0.11 | 25 |
| Chondropsin D | 0.53 | 0.07 | 8 |
| 73-Deoxychondropsin A | 3.0 | 0.10 | 30 |
| Dimethylchondropsin A | 0.43 | 0.04 | 11 |
| Poecillastrin A | 8.0 | 0.40 | 20 |

inhibits the fungal enzyme as compared with the mammalian enzyme. These properties give rise to a question: if chondropsin A is a weaker inhibitor of V-ATPase activity than salicylihalamide and the other inhibitors in Table I, why was it equally as effective in preventing growth of tumor cells? The answer is

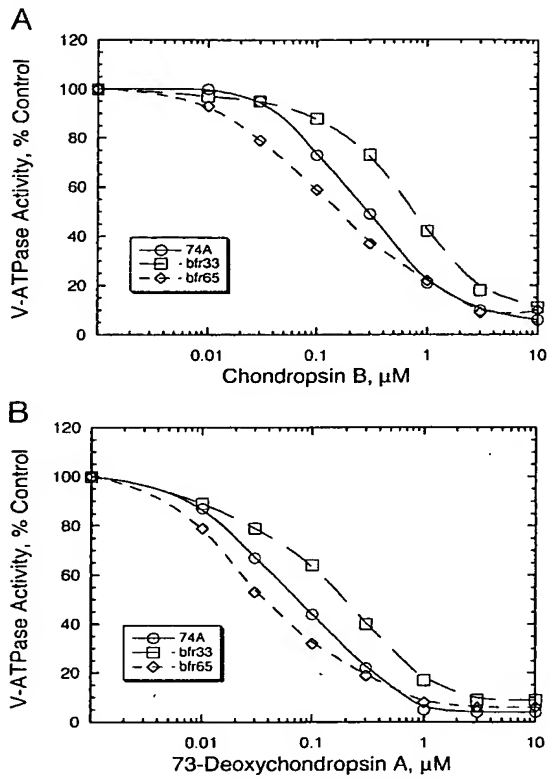



FIG. 4. **The chondropsins have altered affinities for mutant V-ATPases of *N. crassa*.** The effect of two chondropsins on V-ATPase activity in vacuolar membranes (2 μg of protein) from the wild type (*74A*) and two bafilomycin-resistant mutants, bfr33 (T32I) and bfr65 (Y143N), was assayed at 37 °C. Specific activities in the absence of inhibitor were 5.0 μmol/min/mg for strain 74A, 2.3 μmol/min/mg for bfr33, and 3.0 μmol/min/mg for bfr65. Values for half-maximal inhibition are summarized in Table III. *A*, chondropsin B. *B*, 73-deoxychondropsin A.

TABLE III
*Effect of chondropsins on mutant V-ATPases of N. crassa*
The data are derived from Fig. 4, *A* and *B*.

| Strain | Chondropsin B $K_i$ | 73-Deoxychondropsin A $K_i$ |
|---|---|---|
| | μM | μM |
| 74A | 0.25 | 0.065 |
| bfr33 | 0.61 | 0.162 |
| bfr65 | 0.13 | 0.030 |

likely to be found in the complexity of mammalian V-ATPases, which exist in a multitude of forms that may vary in sensitivity to these drugs. Isoforms of genes encoding most of the V-ATPase subunits and examples of alternative splicing have been reported (37). For example, two laboratories found evidence for three distinct isoforms of the 100-kDa subunit a, multiple alternatively spliced variants of two of the isoforms, and tissue-specific expression of these isoforms in the mouse (38, 39). We speculate that chondropsin A is effective against tumor cells because it targets V-ATPases that may subtly differ in structure from the chromaffin granule enzyme tested in our experiments.

The enhanced sensitivity of the fungal V-ATPase relative to the chromaffin granule V-ATPase to inhibition by chondropsins suggests that it may be possible to design molecules that inhibit specific V-ATPases. Although not so dramatic as the all or none response seen with the salicylihalamide family and the animal *versus* fungal V-ATPases (3), it is conceivable that de-

rivatives of chondropsins could be useful as antifungal agents. Developing a drug to target fungi could take advantage of the fact that many fungi lack isoforms and alternatively spliced gene products for the V-ATPase. The genomes of *N. crassa* and *Schizosaccharomyces pombe* contain a single gene for each subunit of the V-ATPase, suggesting the same form of the enzyme is present in all cell membranes. *S. cerevisiae* is slightly more complicated, with an isoform for *VPH1*, named *STV1*, that encodes subunit a, thus giving rise to two forms of the V-ATPase believed to be in two different cellular locations (40–42). The challenge would be in increasing the differential sensitivity between the V-ATPases of the fungal target and the mammalian host cells to an acceptable level.

Two kinds of experiments have identified subunit c of the V-ATPase as the binding site of bafilomycin and concanamycin. Huss *et al.* (43) showed binding of a radiolabeled derivative of concanamycin to subunit c of the *Manduca sexta* enzyme. We identified mutations in subunit c of *N. crassa* that conferred resistance to bafilomycin on the enzyme (24). Although the original mutant V-ATPases were only weakly resistant to concanamycin, our subsequent genetic analyses have indicated that both inhibitors bind the same region of the c subunit, if not the identical site.[2] A surprise was that the sites in the V-ATPase that confer resistance to bafilomycin are identical to homologous sites in subunit c of the F-ATPase that confer resistance to oligomycin (44, 45).

We proposed a common mechanism for the action of these different antibiotics on the V- and F-ATPases (24). The antibiotic binding site appears to be largely on the c subunits, at the critical interface with subunit a. High affinity binding of antibiotic could act like a "stone in the gears," preventing conformational changes within the c subunit or rotation of the ring of c subunits against subunit a. In the current work two mutations that affected the binding of bafilomycin to subunit c were tested for their effects on inhibition by the chondropsins. One mutation resulted in 2.5-fold resistance; one mutation caused a 2-fold enhancement in sensitivity (Fig. 4, *A* and *B*, Table III). Although small, these effects might suggest that the chondropsins also act by blocking the rotation of the c subunits.

Differences in the sequence of subunit c could partly explain the relative insensitivity of the chromaffin granule V-ATPase to chondropsins. Our preliminary data have allowed us to construct a model of the bafilomycin binding site, formed in part by a pocket at the interface of helices 1, 2, and 4.[2] The bovine sequence has three differences on the face of helix 2. The equivalent of Val-55 is Ile; of Val-51, Met; and of Ile-58, Val. However, differences in subunit c are unlikely to explain the different sensitivity of different types of tumor cells. Analysis of sequence data bases indicates that bovine and human cells contain only one gene for subunit c. Either the chondropsins bind to another site or an additional subunit, such as subunit a, forms part of the binding site, as observed for oligomycin binding in the F-type ATPase.

It is interesting that such a wide variety of natural products have evolved to target the V-ATPase. Inhibition of the V-ATPase may be a quick-acting way to disrupt vital cell functions. However, it is equally curious that natural products of similar potency have not been found as inhibitors of the ubiquitous P-ATPases. Perhaps the complex rotary mechanism of V- (and F-) ATPases requires protein structures that are vulnerable targets for a wide range of antibiotics.

[2] B. J. Bowman and E. J. Bowman, unpublished results.

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